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09/204,427	12/03/1998	HEDI HADDADA	8076.102USC1	5504

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/04/2002

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/204,427	Applicant(s) HADDADA ET AL.	
	Examiner Michael Wilson	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Applicant's arguments filed 7-03-02, paper number 22, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 19-22 have been canceled. Claims 23-25 have been added. Claims 15-18 and 23-25 are pending and under consideration in the instant invention. It is noted that the marked up copy of the claims as amended has numerous errors (e.g. claim 15, (a) in clean copy is b) in the marked up version; claim 15, b), i) has a period between E1A and E1B; claim 15, b), i) has EIA and EIB instead of E1A and E1B).

Claim Rejections - 35 USC § 112

1. Claims 15-18 remain rejected and claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The rejection of "a pharmaceutical composition" comprising an adenovirus and "a pharmaceutically acceptable vehicle" (claims 15, 21) as not having support in the specification as originally filed is withdrawn in view of applicants arguments.

Claims 15 and 18 remain rejected and claim 24 is rejected because the limitation of an "endogenous" or "heterologous" promoter (claims 15, 18) does not have support in the specification as originally filed. Applicants argue pg 2, lines 20-23, provide support. Applicants argument is not persuasive. The citation states that a coding sequences is "under the control of a promoter present in or previously inserted into the abovementioned genomic sequence." A heterologous or endogenous promoter has a greater scope than the promoter "present in or previously inserted into the abovementioned genomic sequence." Heterologous and endogenous are relative terms and the claims are not limited to promoters that are heterologous or endogenous to any adenovirus or the adenovirus used to make the vector in the claim. Therefore, the claim has a broader scope of promoters than contemplated in the specification as originally filed.

Claim 25 is new matter. Applicants point to pg 13, lines 5-10, and pg 6, lines 6-7, for support for the claim. Applicants argument is not persuasive. Pg 13 contemplates administering a combination of Ad-IL-2 and Ad-GM-CSF, i.e. two different adenoviral vectors encoding different proteins. The specification does not contemplate one adenoviral vector encoding IL-2 and GM-CSF as claimed. Pg 6 merely states "In combination with IL-2 and IL-4, GM-CSF is an important antitumor factor." It does not state one vector encodes IL-2 and GM-CSF. Nor does the specification state each coding region is operably linked to its own promoter. Nor does the specification state the IL-2 coding region is placed after the GM-CSF coding region.

2. Claims 15-18 remain rejected and claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The specification as originally filed does not provide adequate written description for replication defective adenoviruses encoding IL-2, γ-IFN or GM-CSF operatively linked to an early E1A or "heterologous" promoter used to treat a tumor in a patient. An adequate written description of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is a description of the promoters and a description of how to make the adenovirus. It is not sufficient to define an adenoviral vector for gene therapy solely by its principal biological property, i.e. to treat a tumor in a patient when injected intratumorally or into cells that infiltrate tumors, because disclosure of no more than that is simply a wish to identify adenoviral vectors with the DNA encoding the cytokine operably linked to an early or "heterologous" promoter having that biological property. Thus, claiming all replication defective adenoviral vectors encoding a cytokine operably linked to an early promoter or "heterologous" promoter that are able to treat a tumor without defining the promoters or how to make such vectors is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Likewise the specification does not provide adequate written description for replication defective adenoviruses encoding GM-CSF and IL-2 used to treat a tumor in a patient. The specification does not teach a vector encoding two copies of one cytokine, two different cytokines or how the copies are operably linked to promoters. The specification does not teach the combination of cytokines in a vector required to treat tumors administered as claimed or the resulting therapeutic effect. An adequate written description of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is a description of the combination of elements and a description of the resulting effect. Therefore, claim 25 lacks written description.

Applicants argue the examiner has not provided any reasons why the skilled artisan would not deem the inventor had possession of vectors encoding cytokines operably linked to the E1A promoter or a "heterologous promoter". Applicants argument is not persuasive. The basis of the rejection is that adenoviral vectors encoding cytokines operably linked to the E1A promoter or a "heterologous promoter" as claimed that are capable of treating tumors as claimed are not adequately described in the specification, and is clearly set forth in the reiterated paragraph above. Adenoviral vectors encoding IL-2 or γ-IFN operably linked to the E1A promoter or a "heterologous promoter" capable of treating tumors were not well-established. Procedures for administering adenoviral vectors encoding cytokines operably linked to the E1A promoter or a "heterologous promoter" capable of treating tumors were not well-established. Adenoviral vectors encoding GM-CSF capable of treating tumors, and methods of using such

vectors to treat tumors were not well-established. The mere suggestion of replacing the adenoviral late promoter with the CMV, RSV or E1A promoter (pg 14) is not adequate guidance for one of skill to use the vector to treat tumors as claimed. The specification does not even mention an adenoviral vector encoding GM-CSF. As such, the claims are rejected for reasons of record.

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3. Claims 15-18 remain rejected and claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a replication-defective adenoviral vector intratumorally to a patient such that growth of the tumor is inhibited, wherein said vector encodes IL-2 or γ-IFN operably linked to the adenoviral late promoter, does not reasonably provide enablement for using an adenoviral vector encoding GM-CSF to treat tumors, using any "endogenous or heterologous" promoter, the CMV promoter or the E1A promoter to treat tumors in context of the claim, or an adenoviral vector encoding GM-CSF and IL-2 to treat tumors as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The combination of promoter, DNA encoding a cytokine and route of administration required to obtain a therapeutic effect against a tumor using adenoviral gene therapy *in vivo* was unpredictable at the time the invention was made. In particular, it was unpredictable how to target adenoviral vectors to tumors *in vivo* using any route of administration. Miller (1995,

FASEB J., Vol. 9, pages 190-199) reviewed adenoviral vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 192, col. 2; page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy continues to be the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviewed adenoviral vectors known in the art for use in gene therapy and discusses problems associated with them (page 241, col. 1). Verma indicated a resolution to vector targeting has not been achieved in the art (see entire article). Crystal (1995, Science, Vol. 270, page 404-410) also reviewed adenoviral vectors known in the art and indicated that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (para. bridging pages 404-405; page 406, col. 2, line 7; page 409).

Viral vectors encoding IL-2 and γ-IFN administered intratumorally to inhibit tumor growth were known in the art at the time the invention was made (Nabel, US Patent 6,297,219, Oct. 2, 2001; Barber, US Patent 5,662,896, Sept. 2, 1997). Replication defective adenoviral vectors encoding protein operably linked to the late promoter used to obtain protein expression *in*

vivo were known in the art at the time the invention was made (Crystal, US Patent 6,013,638, Jan. 11, 2000; Rosenfeld, 1991, Science, Vol. 252, pages 431-434). The art at the time of filing did not teach administering adenoviral vectors *in vivo* by any mode of delivery such that "cells which infiltrate said tumor" were targeted, infecting "cells which infiltrate said tumor" *ex vivo* with an adenoviral vector and administering the cells into the patient such that a therapeutic effect was obtained, using a vector encoding IL-1, IL-3, IL-4, IL-5, IL-6, α-IFN, TNF or CSF to treat tumors, or using an adenoviral vector encoding the cytokine operably linked to an early or "heterologous" promoter to treat tumors.

The specification teaches direct injection of "the vector" carrying IL-2 into tumors leads to tumor regression (para. bridging pages 12 and 13) which is assumed to be the adenovirus encoding a cytokine operably linked to the late promoter described in the paragraph bridging pages 9 and 10. The specification does not teach administering a viral vector into a remote site such that cells that infiltrate the tumor are targeted. Nor does the specification teach administering a viral vector into a remote site or directly injecting cells infected *ex vivo* into a tumor such that a therapeutic effect is obtained. Without such guidance, it would require one of skill undue experimentation to determine modes of delivery other than intratumoral injection that target tumor cells and provide a therapeutic effect.

The specification does not enable using a adenoviral vector encoding GM-CSF (claim 24) to treat tumors because the specification does not teach the level of GM-CSF required to obtain a therapeutic effect or correlate the level of expression of IL-2 or γ-IFN known in the art to inhibit

tumor growth with the level of GM-CSF required to obtain an equivalent effect. Without such guidance, it would require one of skill undue experimentation to determine how to use any cytokines other than IL-2 or γ-IFN to treat tumor cells as claimed.

The specification does not enable one of skill in the art at the time the invention was made to use an adenoviral vector comprising DNA encoding a IL-2 or γ-IFN operably linked to an adenoviral "heterologous" promoters (claims 15 and 24) or CMV (claim 23) to treat tumors. The specification lists the RSV LTR, the IE promoter of CMV, and MMTV or metallothionin inducible promoters as possible replacements for the adenovirus late promoter (pg 14, lines 4-11). However, the specification and the art at the time of filing did not teach the RSV LTR, the IE promoter of CMV, MMTV or metallothionin inducible promoters provided adequate expression of a protein in an adenoviral vector used *in vivo* to obtain a therapeutic effect. Nor does the specification correlate the amount of expression obtained using the adenoviral late promoter to expression obtained using the RSV LTR, the IE promoter of CMV, and MMTV or metallothionin inducible promoters such that equivalent levels of expression would be expected. Therefore, the specification does not overcome the unpredictability in the art regarding the promoter to use with adenoviral vectors administered into a tumor that provided a therapeutic level of expression of a protein. While a showing of an equivalent expression of a cytokine using promoters other than the late promoter is not necessary to achieve a therapeutic effect, in view of the unpredictability in the art regarding promoters used to target specific tissues for gene therapy, and the lack of teachings in the art regarding using these promoters with adenoviral vectors to

obtain a therapeutic effect *in vivo*, the specification must provide some correlation between the late promoter and other promoters to enable a claim encompassing using any "endogenous or heterologous promoter" in an adenoviral vector to treat tumors. Such a correlation cannot be found in the instant specification.

Applicants point to Slos as illustrating that other promoters were used in defective adenoviral vectors resulting in tumor regression. Applicants argument is not persuasive. Slos was not available at the time of filing. In addition, the vector encoding IL-2 operably linked to the RSV promoter also had a deletion in E4 which is not disclosed in the instant application. Therefore, the vector encoding IL-2 operably linked to the RSV promoter taught by Slos does not correlate to the disclosed invention.

Applicants point to Ahmed as illustrating that other promoters were used in defective adenoviral vectors resulting in tumor regression. Applicants argument is not persuasive. Ahmed was not available at the time of filing. Nor was the adenoviral vector used as the backbone (see pg 78, col. 1, first full para., Wills 1994). In addition, the vector encoding IL-2 operably linked to the CMV promoter also had a deletion in E4 which is not disclosed in the instant application. Therefore, the vector encoding IL-2 operably linked to the RSV promoter taught by Ahmed does not correlate to the disclosed invention.

Applicants point to Stewart of record (1999, Gene Therapy, Vol. 6, pg 350-363) as illustrating that other promoters were used in defective adenoviral vectors resulting in tumor regression. Applicants argument is not persuasive. Stewart was not available at the time of

filing and does not teach the vector encoded IL-2 operably linked to the CMV promoter or that the E1 and E3 regions were deleted. Therefore, the adenoviral vector encoding IL-2 taught by Stewart does not correlate to the disclosed invention.

The specification does not enable using any "endogenous promoter" (claims 15 and 24) or the E1A promoter (claim 16) such that therapeutic levels of expression of IL-2 or γ-IFN could be obtained *in vivo*. The specification lists the E1A promoter as a possible replacement for the adenovirus late promoter (pg 14, lines 16-22). However, the specification and the art at the time of filing did not teach the E1A promoter provided adequate expression of a protein in an adenoviral vector used *in vivo* to obtain a therapeutic effect. Nor does the specification correlate the amount of expression obtained using the adenoviral late promoter to expression obtained using the E1A promoter such that equivalent levels of expression would be expected. Therefore, the specification does not overcome the unpredictability in the art regarding the promoter to use with adenoviral vectors administered into a tumor that provided a therapeutic level of expression of a protein. While a showing of an equivalent expression of a cytokine using promoters other than the late promoter is not necessary to achieve a therapeutic effect, in view of the unpredictability in the art regarding promoters used to target specific tissues for gene therapy, there must be some correlation between the late promoter and the E1A promoter to enable a claim reciting using any "endogenous" promoter or the E1A promoter in an adenoviral vector to treat tumors.

The specification does not teach a vector encoding GM-CSF and IL-2 (claim 25) or how the DNA encoding the cytokines are operably linked to promoters. The specification does not teach the combination of cytokines required to treat tumors using adenoviral vectors administered as claimed or the resulting therapeutic effect. Enablement of such adenoviruses requires more than a mere statement that it is part of the invention and reference to a potential method for making it; what is required is adequate guidance regarding the combination of elements and the resulting effect. Without such guidance, it would have required one of skill undue experimentation to determine how to use an adenoviral vector encoding two or more cytokines to treat tumors.

Applicants argue it would not have been undue experimentation to determine the amount of GM-CSF required to obtain a therapeutic effect. Applicants argument is not persuasive in view of the unpredictability in the art taken with the lack of guidance in the specification or the art at the time of filing regarding the level of GM-CSF expression required to obtain a therapeutic effect using an adenoviral vector injected directly into the tumor.

Applicants provide Fujii and state Fujii taught similar amounts of injected cells as those taught in the specification. Applicants argument is not persuasive because the specification taught injecting vector alone in the absence of cells. In addition, the vector of Fujii does not correlate to the vector disclosed in the instant application because it has the GM-CSF coding region operably linked to the β-actin promoter which was not disclosed in the instant application. Applicants point to page 12 as providing guidance for quantification of the cytokines using

ELISAs. Applicants argument is not persuasive because the specification does not teach the amount of GM-CSF required to treat tumors using the claimed invention.

Applicants statement on pg 14, that "If results are in fact achieved as the Examiner has admitted on record with IL-2 or γ-IFN, Applicants submits that other cytokines in combination would easily achieve the therapeutic effect" is unclear. However, the specification does not teach making or using an adenoviral vector encoding GM-CSF and IL-2 to treat tumors. In addition, the specification does not enable using an adenoviral vector encoding GM-CSF in the claimed invention for reasons cited above; therefore, the specification does not enable using an adenoviral vector encoding GM-CSF and IL-2 in the claimed invention. While the specification enables using an adenoviral vector encoding IL-2 in the claimed invention, the specification does not provide an enabled use for using an adenoviral vector encoding IL-2 and GM-CSF to treat tumors. Without such guidance, it would require one of skill undue experimentation to determine how to make and/or use an adenoviral vector encoding GM-CSF and IL-2 to treat tumors as claimed.

4. Claims 15-18 remain rejected and claims 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claims 15 and 21 are indefinite because part (a)(i) requires the adenovirus is replication-defective and lacks E1A, E1B and E3. An adenovirus lacking E1A, E1B and E3 is replication-

defective; therefore, the limitation of "replication-defective" does not further limit the claim.

Claims 15 and 21 are indefinite because "said adenovirus" lacks antecedent basis.

Claims 15 and 21 would be more clear if stated --(a) a replication-defective adenoviral vector lacking the E1A, E1B and E3 regions; and...--.

Claim 16 remains indefinite because it does not further limit claim 15. An adenoviral vector cannot lack the E1A region as in claim 15 while retaining the early promoter of the E1A region as in claim 16. Applicants argue the claims have been amended to overcome the rejection. Applicants argument is not persuasive.

Claim Rejections - 35 USC § 103

5. The rejection of claims 15-18 under 35 U.S.C. 103(a) as being unpatentable over Barber (US Patent 5,662,896, Sept. 2, 1997) in view of Rosenfeld (1991, Science, Vol. 252, pages 431-434) is withdrawn.

Applicants argue Barber cannot be used because the priority documents of Barber do not support intratumoral injection. Applicants argument is persuasive. Upon review of applicants priority documents, it has been determined that the claimed invention in the instant application has priority back to 3-16-92, the filing date of FR 9203120, now issued as publication number 2 688 514. Upon review of the priority documents of Barber ('892), it has been determined that applications 07/965,084, filed 10-22-92, and 07/565,606, filed 8-10-90, taught infecting only the target cells (see for example, pg 9 of '606, lines 5-17, especially lines 9-11), and using tissue-

specific promoters, but '084 and '606 did not support directly injecting tumors. Since lost application 07/965,084 is a continuation of 07/586,603, the disclosures of '084 and '603 are identical. Therefore, the priority date of Barber is 3-17-93, the filing date of 08/032846, now US Patent 5,662,892. Since applicants have priority back to 3-16-92, and the priority date of Barber (3-17-93) is after applicants priority date, Barber is not available as prior art.

6. Claims 15-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Nabel (US Patent 6,297,219, Oct. 2, 2001) in view of Crystal (US Patent 6,013,638, Jan. 11, 2000) for reasons of record.

Nabel taught administering an adenoviral vector encoding IL-2 or γ-IFN in a pharmaceutically acceptable carrier intratumorally (claims 1, 9, 13). Nabel did not teach the adenoviral vector had a deletion in E1A, E1B and E3. However, at the time of filing, Crystal taught an adenoviral vector with a deletion in E1A, E1B and E3 encoding a protein operably linked to the adenoviral late promoter (Fig.1, claim 1). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer an adenoviral vector encoding IL-2 or γ-IFN in a pharmaceutically acceptable carrier intratumorally as taught by Nabel using the replication defective adenoviral vector of Crystal. One of ordinary skill in the art at the time the invention was made would have been motivated to delete E1A, E1B and E3 as taught by Crystal in the method of Nabel to decrease the replication of the adenovirus *in vivo* and because Crystal taught the replication defective adenovirus expressed protein *in vivo*. The late

promoter is a "heterologous" promoter (claim 18) because the adenoviral late promoter is heterologous to the cytokine.

Applicants argue there is no working example of record in Nabel that intratumoral administration of cytokine-expressing adenoviral vectors work *in vivo* to provide tumor inhibition. Applicants argument is moot because the claims do not require tumor inhibition, and because Nabel has claims to directly administering an adenoviral vector encoding IL-2 into a tumor (1, 9, 13).

Applicants argue Nable does not have priority back to 3-31-89, the filing date of 07/331,366. Therefore, Applicants argue Nabel is not persuasive because Nabel has priority back to at least 6-28-91, the filing date of priority document 07/724,509, which is before applicants effective filing date.

Applicants argue Nabel does not teach the vector lacks E1A, E1B and E3, that the vector penetrates a tumor. Applicants argument is moot because Nabel need not teach all the limitations of the claim, because Crystal taught the vector lacks E1A, E1B and E3, because the claims do not require the vector penetrates the tumor, and because Nabel taught directly injecting the adenoviral vector into the tumor which is penetrating the tumor.

Applicants argue Nable does not provide a reasonable expectation of achieving cytokine expression with an adenoviral vector. Applicants argument is not persuasive because Nable has a claim to directly injecting an adenoviral vector encoding a cytokine into a tumor such that the cytokine is expressed.

Applicants argue the method of Crystal differs from the method of intratumoral administration. Applicants argument is moot because Crystal is not relied upon as teaching intratumoral injection.

Applicants reiteration of tumor tissue being highly disorganized and heterogeneous (para. bridging pg 19-20 of the response) is moot because Nable taught directly injecting the adenoviral vector into the tumor which is penetrating the tumor.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

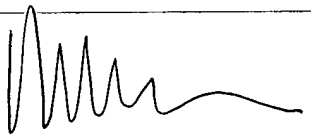
Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER